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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/743,885	10/22/2001	Jantina Creemers	U 013212-4	8619

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EXAMINER	
BAUM, STUART F	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/743,885	CREEMERS ET AL.	
	Examiner	Art Unit	
	Stuart F. Baum	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/12/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-32 are pending.

2. Applicant's election with traverse of Group IV, claims 20-21 in the reply filed on 11/3/2004 is acknowledged. The traversal is on the ground(s) that the claims of Group IV should be together with claims 12-14 of Group II and claim 30 of Group V as per Annex B of the Administrative Instructions under the PCT at subparagraph (e)(i). Applicants also contend that the double stranded DNA molecule and the resultant recombinant gene product should be grouped together, as per Example 17 of Annex B, Part 2 (page 14, 1st paragraph of response).

This is not found persuasive because the Lack of Unity requirement mailed 6/30/2004 groups the first product claims, i.e., claims to the isolated DNA sequence encoding a protein, with the first method of using the product, i.e., a process for producing a transgenic plant exhibiting a modified nectar and a process for producing honey from said modified nectar. The claims in Example 17 are directed to a specific protein and a specific DNA sequence that encodes said protein. Applicants claims are broadly drawn to a nucleic acid sequence encoding a protein that exhibits at least 60% homology to the amino acid sequence set forth in SEQ ID NO:1. Therefore, Applicants' claim is drawn to many nucleic acid sequences and many amino acid sequences which is not congruent with Example 17.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-19, and 22-30 are withdrawn from consideration for being drawn to non-elected inventions.

Claims 31 and 32 have been newly added and are directed to the elected invention.

3. Claims 20-21 and 31-32 including SEQ ID NO:1 are examined in the present office action.

Specification

4. Objection is made to the specification for not incorporating SEQ ID NO's when referring to nucleic acid or amino acid sequences. 37 CFR 1.821(d) requires the use of the assigned sequence identifier (e.g. SEQ I.D. NO: X) in all instances where the description or claims of a patent application discuss sequences. In the instant application, Applicants disclose nucleic acid and amino acid sequences in Figures 2-4, 7, 12-15, and 19 which are not referenced by SEQ ID NO's in the Brief Description of the Drawings.

On page 2, line 18, "endoplasmic" is misspelled.

Drawings

5. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the current Figure 5A-5B does not disclose any discernable data. The Figure is totally black. Correction is requested.

Claim Objection

6. Claims 20, and 31-32 are objected to for depending on non-elected claims. For purposes of compact prosecution, claims 20, and 30-31 will be interpreted to contain all the limitations of the claims from which they are dependent. Correction is requested.

Written Description

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 20-21, and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a process for producing a recombinant gene product from honey comprising producing a transgenic plant by introducing into a plant cell a recombinant-double-stranded DNA molecule comprising a promoter functional in nectaries of plants, or an isolated DNA sequence from the promoter region upstream of a nectary-specific expressed sequence which encodes a protein that has at least 60% homology to the amino acid sequence given in SEQ ID NO:1, and a DNA sequence encoding a signal peptide that targets the recombinant protein to nectar, or a DNA sequence encoding a signal peptide that targets the recombinant protein to nectar wherein the DNA sequence isolated from a nucleic acid encoding a protein that is expressed in nectaries; or a process for producing a metabolite from honey comprising producing a plant that excretes the metabolite in nectar and which plant has been produced by breeding and selection. The Office interprets the word "homology" to mean sequence identity.

Applicants disclose the isolation of the NEC1 cDNA using the mRNA Differential Display System (pages 18-20, Example 1) using RNA isolated from nectaries, sepals, petals

stamens, and pistils from Petunia. Applicants disclose the full length sequence is 1205 basepairs encoding a polypeptide of 265 amino acids (page 20, lines 7-10). The promoter fragment of NEC1 was cloned using the genome walker protocol and the sequence is disclosed in SEQ ID NO:7 (page 23, Example 5) and NEC1 is mainly expressed in the nectaries (page 22, Example 4). Applicants determined that two proteins, CVH29 and CVH50, which are constituents of honey are also constituents of heather nectar (pages 25-26, Example 10). Applicants disclose a putative signal sequence of 17 amino acids from the CVH29 protein, is set forth in SEQ ID NO:6 (page 27, Example 12).

The Applicants do not identify essential regions of the NEC1 promoter or the CVH29 signal sequence whose sequences are set forth in SEQ ID NO:7 and 6, respectively, nor do Applicants describe any promoter sequence from any protein exhibiting 60% homology to SEQ ID NO:1, nor do Applicants describe a genus of signal peptides that targets recombinant proteins to nectar. Applicants also do not describe any plant that excretes a metabolite in nectar that has been produced by breeding and selection. In addition, Applicants do not identify structural, genotypic or phenotypic features of the claimed plants.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In summary, the court stated that a written description of an invention requires a precise definition, one that defines the structural features of the chemical genus that distinguishes it from other chemical structures. A definition by function does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. The court goes on to say, "A description of a genus of

cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." *See University of California v. Eli Lilly and Co.*, 119 F.3d 1559; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants fail to describe a representative number of polynucleotide sequences encoding a promoter functional in nectaries, or a promoter from a nucleic acid encoding a protein exhibiting at least 60% homology to SEQ ID NO:1, or a DNA sequence encoding a signal peptide that targets a recombinant protein to nectar, or a DNA sequence encoding a signal peptide from a protein normally expressed in nectaries, or any plant that excretes a metabolite in nectar which has been produced by breeding and selection. Applicants only describe a promoter of SEQ ID NO:7 and a nucleic acid of SEQ ID NO:6 that encodes a putative signal peptide for targeting proteins to nectar. Furthermore, Applicants fail to describe structural features common to members of the claimed genus of polynucleotides. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*.

Furthermore, given the lack of description of the necessary elements essential for the promoter or signal sequence, it remains unclear what features identify a promoter that directs expression in any nectary, or a promoter from a nucleic acid encoding a protein exhibiting 60% homology to SEQ ID NO:1, or a signal sequence that targets proteins to any nectar. Since the genus of promoters that express in nectaries and signal sequences that target proteins to any nectar have not been described by specific structural features, the specification fails to provide an adequate written description to support the breath of the claims. In addition, since Applicants

have not described a plant that excretes a metabolite in nectar which has been produced by breeding and selection, by a genotype, phenotype or specific structural features, the specification fails to provide an adequate written description to support the generic claims.

Enablement

8. Claims 20-21 and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands,* 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The claims are drawn to a process for producing a recombinant gene product from honey comprising producing a transgenic plant by introducing into a plant cell a recombinant-double-stranded DNA molecule comprising a promoter functional in nectaries of plants, or an isolated DNA sequence from the promoter region upstream of a nectary-specific expressed sequence which encodes a protein that has at least 60% homology to the amino acid sequence given in

SEQ ID NO:1, and a DNA sequence encoding a signal peptide that targets the recombinant protein to nectar, or a DNA sequence encoding a signal peptide that targets the recombinant protein to nectar wherein the DNA sequence is isolated from a nucleic acid encoding a protein that is expressed in nectaries; or a process for producing a metabolite from honey comprising producing a plant that excretes the metabolite in nectar and which plant has been produced by breeding and selection. The Office interprets the word "homology" to mean sequence identity.

Applicants disclose the isolation of the NEC1 cDNA using the mRNA Differential Display System (pages 18-20, Example 1) using RNA isolated from nectaries, sepals, petals stamens, and pistils from Petunia. Applicants disclose the full length sequence is 1205 basepairs encoding a polypeptide of 265 amino acids (page 20, lines 7-10). The promoter fragment of NEC1 was cloned using the genome walker protocol and the sequence is disclosed in SEQ ID NO:7 (page 23, Example 5) and NEC1 is mainly expressed in the nectaries (page 22, Example 4). Applicants determined that two proteins, CVH29 and CVH50, which are constituents of honey are also constituents of heather nectar (pages 25-26, Example 10). Applicants disclose a putative signal sequence of 17 amino acids from the CVH29 protein, is set forth in SEQ ID NO:6 (page 27, Example 12). Applicants disclose the construction of an expression cassette for excretion of proteins in nectar comprising the NEC1 promoter and operably linked to a nucleic acid encoding the CVH29 signal sequence of SEQ ID NO:6 (pages 28-30, Example 13).

Applicants have not disclosed the isolation of proteins or metabolites from honey made with nectar generated by plants that had been transformed with Applicants' expression cassette. It is unclear if a recombinant protein that is expressed in cells of the nectary will be detectable in honey, given that honey is produced by bees, that in addition to other procedures, add enzymes

from their saliva to the nectar solution. Applicants have not disclosed how one skilled in the art, produces a metabolite in a nectary cell and then targets that metabolite to the nectar. Applicants have not disclosed a breeding program or selection method for producing a plant that excretes a metabolite in nectar.

Applicants have not disclosed how one makes or isolates any of the sequences that are encompassed by Applicants' broad claims. Applicants have not taught which regions of the respective polynucleotides can be used to amplify any of said polynucleotides or which regions can be used as a probe to isolate any of said polynucleotide sequences.

The state-of-the-art teaches that promoter sequences exhibiting less than 100% sequence identity to the full length promoter sequence produce unexpected results. Benfey et al (1990, Science 250:959-966) teach that the 35S CaMV promoter consists of domains that individually regulate spatial expression within plants. "The combination of each of the five B subdomains with domain A results in an expression pattern that differs from that of the individual subdomains or domain A" (page 961, left column, 2nd paragraph). In other words, deleting a required domain will jeopardize the proper spatial and temporal expression pattern. In addition, Benfey et al (1989, EMBO J, 8(8):2195-2202; page 2200, left column 2nd paragraph) teach that not only are the promoter domains important for specifying proper spatial and temporal expression but that when all domains were present, the quantity of expression increased.

Applicants' claims are drawn to any promoter functional in nectaries of plants but the state-of-the-art teaches nectary position is variable. Baum et al (2001, Development 128:4657-4667) teach that the location of nectaries within flowers is variable, with nectaries arising at any position along the receptacle or associated with any of the four floral organs (page 4657, right

column, lines 2-4). In addition, using a promoter isolated from one species of plant would produce unpredictable results when said promoter is used to specify expression of a gene in another species of plant. Oommenn et al (1994, The Plant Cell 6:1789-1803) teach that the alfalfa isoflavone reductase promoter exhibits a different expression pattern in tobacco as compared to the expression in alfalfa. In tobacco, the alfalfa isoflavone reductase promoter expressed in vegetative tissues and in reproductive organs whereas the same construct only expressed in the root meristem, cortex and nodules of alfalfa plants (abstract).

Applicants' claims are also drawn to any nucleic acid encoding any signal peptide that targets the recombinant protein to nectar. But, Applicants' own admitted statement of the prior art teaches that nectar is secreted from secretory cells either via the cell membrane (eccrine secretion) or via the Golgi and endoplasmic reticulum vesicles (granulocrine secretion) (page 2, 16-19). Therefore, it is unclear if a nucleic acid encoding a signal peptide that targets proteins to the cell membrane will also target said protein to the nectar, and the same is true for nucleic acids encoding a signal peptide to the endoplasmic reticulum. In addition, Applicants have not disclosed that a nucleic acid encoding a signal peptide which operates to target a protein to the nectar of one plant will also target a protein to the nectar of another species of plant given Applicants' own admission that research on the molecular regulation of nectary development and nectary biochemistry has not been reported (page 2, lines 19-20).

In the absence of guidance, undue trial and error experimentation would be required for one of ordinary skill in the art to screen through the multitude of non-exemplified sequences, either by randomly isolating promoters and nucleic acid molecules that encode signal peptides, or by using non-disclosed fragments of SEQ ID NO:6 or 7 as probes or by designing primers to

undisclosed regions of SEQ ID NO:6 or 7 and isolating or amplifying fragments, subcloning the fragments, producing expression vectors comprising a putative promoter that directs expression in a nectary cell and comprising a nucleic acid sequence encoding a signal peptide that targets proteins to the nectar, and transforming plants therewith, and then allowing bees to collect nectar from said plants and analyzing honey made from said nectar in order to identify those, if any, that are able to be used to over-express a protein in nectar which is subsequently made into honey by said bees and said protein is isolated and purified from the honey. In addition, undue trial and error experimentation would be required for one of ordinary skill in the art to produce a plant that excretes a metabolite in nectar wherein said plant has been produced by breeding and selection, given that Applicants have not provided any guidance for producing said plant.

Therefore, given the breadth of the claims; the lack of guidance and examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue experimentation would be required to practice the claimed invention, and therefore the invention is not enabled.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart F. Baum whose telephone number is 571-272-0792. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Stuart F. Baum Ph.D.
Patent Examiner
Art Unit 1638
December 29, 2004

AMY J. NELSON, PH.D
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